

PATENT SPECIFICATION

NO DRAWINGS

L132,233



Date of Application and filing Complete Specification: 22 Oct., 1965.

No. 20826/65.

Complete Specification Published: 30 Oct., 1968.

© Crown Copyright 1968.

Index at acceptance:—A5 B(2C, 2G, 2L, 2P, 2S); C3 P(7C8B, 7C9, 7C14A, 7D2A2B, 7D3, 7K7, 11C8B, 11C9, 11C14A, 11D2A)

Int. Cl.:—A 61 k 3/00

COMPLETE SPECIFICATION

Medicinal Compositions containing Sequestering and Chelating Agents

We, HARVEY ASHMEAD and FLOYD R MENCIMER, both citizens of the United States of America, residing at 719 East Center, Kaysville and 3424 Iowa Avenue, Ogden, respectively,

5 United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the

10 following statement:—

This invention pertains to the use of two or more complexing agents in combination for their synergistic, additive or protective effect in accomplishing the removal of cations and/or 15 cation compounds, that is insoluble or poorly soluble crystalline compounds arising from the reaction of cations, such as calcium, with anions such as carbonate or phosphate from the body of all classes of animals and humans and to 20 effect a favorable influence on the crystalloidal and colloidal systems of the body animals and man.

Heretofore it has been virtually impossible 25 to cause the assimilation of complexing agents such as chelating agents by animals or humans through the digestive system. The problem is multifold in scope with many factors to overcome, such as hydrolyzing of sequestrants into 30 their inactive forms e.g., the ortho form when the sequestrants are phosphates; complexing of sequestrants with cations and elimination thereof in the faeces; and in general the rejection of non-assimilable complexing agents by 35 the selective action of the cells in the lining of the gut.

The presence of aberrant cations in the 40 system of animals and humans has caused many well-known ailments such as calcific gall stones, renal calculi, calcific deposits in bursa, salivary calculi, sclerotic or atherosclerotic plaques or deposits in blood vessels or other organs.

Up to the present time, treatment of these

conditions has not been too successful and in 45 most cases involves the necessity of operations for the removal of these deposits or other painful procedures.

The present invention makes possible the 50 treatment of these deposits without the necessity of operation or painful procedures. This is accomplished by administering a composition orally which prevents a naturally assimilable complexing agent from being inactivated before it can be assimilated in the active form into the systems of humans and animals. The 55 assimilable complexing agent then increases the ability of body fluids to retain aberrant cations in solution, thus preventing growth of undesirable deposits and aiding the dissolution of those already existing.

Therefore, it is an object of the present 60 invention to provide a process whereby naturally assimilable complexing agents can be absorbed more efficiently into the systems of animals.

Another object is to provide a composition 65 for the prevention and treatment of conditions caused by undesirable aberrant cations or cation compounds in the bodies of humans and animals which may be administered orally or parenterally.

Another object is to provide a composition 70 for the treatment of all undesirable types of calcific deposits in the bodies of humans and animals.

A further object is to provide a composition 75 whereby a complexing agent in its active form may be absorbed into the systems of humans and animals when administered orally.

Another object is to provide a composition 80 which will favorably effect the colloidal and crystalloidal systems in the blood and urine of humans and animals.

A further objective is to provide a composition 85 which will overcome the inhibitory effect of aberrant cations on assimilation and utilization.

[P]

tion of various drugs or food by both man and animals.

We have found that, by administering certain compositions (as hereinafter defined) comprising a non-toxic inorganic complexing phosphate (as hereinafter defined) together with a chelating agent (as hereinafter defined) and/or an ion-exchange material (as herein-after defined) we can prevent accumulation of undesirable cations and/or cation compounds and remove aberrant cations and/or cation compounds deposited in animal and human bodies.

This phenomenon results from the fact that one of the complexing agents combines with cations within the gut, thus limiting absorption of these cations by the animal. This action then allows the other complexing agent or agents to be absorbed into the circulatory system in their active form capable of complexing undesirable cations or cation compounds within the body.

For example, it has been found that an excess mole equivalent of a complexing agent over the mole equivalent of cations in the gut leads to the absorption of the surplus complexing agent.

In this manner, the assimilable complexing agents are capable of complexing undesirable cations within the body or the urinary tract thus restoring the mineral equilibrium to normal within the animal's body. Note the lowering of blood phosphorus level in experiment entitled "EFFECT ON WHITE RATS OF PROLONGED INTAKE OF COMPOSITION OF INVENTION IN DRINKING WATER".

Because of their peptizing and deflocculent properties, these agents favourably affect the colloidal and crystalloidal systems in the blood and urine by preventing the formation of undesirable precipitates, aggregates, or accretions. In some instances of urinary diseases it has been found expedient to regulate the pH of the urine to conform with the pH of the particular complexing agent or agents employed to take advantage of their most active form.

Occasionally, we have found it desirable to regulate the daily intake of cations and/or cation compounds by altering the diet of animals and men, thus reducing the amount of agent required to bind these cations in the gut and increase the available amount of free complexing agent for the circulatory system and subsequently the urine.

By utilising these processes undesirable compounds are eliminated in a soluble or colloidal form.

The chelating agents used in the composition of this invention are selected from:—

(I)

The sodium salt of N,N-di(2-hydroxyethyl) glycine

N - (2 - Hydroxyethyl)ethylene diamine tri-acetic acid 65
Trisodium N - (2 - hydroxyethyl) ethylene diamine triacetate.

1,2 diaminocyclohexane tetraacetic acid

Nitrolotriacetic acid

2 hydroxymethyl-5 hydroxy-pyran 70

N,N,N',N' - tetrakis (2 - hydroxypropyl)

ethylene diamine, and

N,N-di-(2-hydroxyethyl) glycine

and (II)

Ethylene diamine tetraacetic acid 75

Pentasodium diethylene triamine penta-acetate

Mono-, di-, tri-, and tetra-sodium salts of ethylene diamine tetraacetic acid

Diethylene triamine pentaacetic acid, and 80

The calcium salt of ethylene diamine tetra-acetic acid.

The non-toxic ion exchange materials used in the composition of this invention are selected from:—

85

(III)

Resins having a carboxylic acid functional group

Sodium alumino-silicate gel

Polystyrene matrix having a nuclear sulfonic acid group as a functional group 90

Hydrocarbon matrix (e.g. poly-divinyl benzene, polystyrene matrix or a copolymer of divinyl benzene and styrene) having phosphonic acid as a functional group

Styrene divinyl benzene copolymer matrices with sulfonic acid functional groups

Styrene divinyl benzene copolymer matrices with quaternary ammonium functional groups

Styrene-divinyl benzene copolymer matrices with polyalkylamine functional groups; and

100

(IV)

Poly-N-vinyl-5-methyl-2 oxazolidinone and copolymers of N-vinyl-5-methyl-2-oxazolidinone (e.g. copolymers with divinyl benzene, styrene and the like). 105

The inorganic phosphates used in the compositions of this invention are selected from:—

Sodium tripolyphosphate, (Form I) 110
Na₅P₃O₁₀

Sodium tripolyphosphate, (Form II)

Na₅P₃O₁₀

Sodium hexametapyrophosphate Na₆P₆O₁₉

Sodium hexametaphosphate

Tetra sodium and potassium pyrophosphate

Na₄P₂O₇ and K₄P₂O₇

S.Q. Phosphate Na₅P₆O₁₀

Sodium acid pyrophosphate

115

The invention provides a composition con- 120

sisting of (a) a phosphate as defined above together with (b) a chelating agent selected from (I) or (II) above and/or (c) an ion exchange material selected from (III) above 5 or (when the chelating agent if present is selected from group (I)) an ion exchange material selected from (IV) above. These compositions may also contain (when the chelating agent is selected from (I) and/or the ion exchange material is selected from (III)) a colloidal carrier which may be sodium carboxymethyl cellulose, carboxymethyl cellulose or other cellulose gum. These compositions may also contain water as a carrier. 10 15 The invention further provides, according to another embodiment, a composition comprising (a) a colloidal carrier and (b) a phosphate as defined above together with (c) a chelating agent selected from (I) above and/or an ion exchange material selected from (IV) above. 20 These compositions may also suitably contain water as a carrier. 25 The dosage range which may be used in all classes of animals and man of the above-described combination is 1 mg/kilogram body weight/day to 1 gram/kilogram body weight/day. 30 The preferred method of application is oral administration of the compositions; however, all or part may be given in tablet, capsule, mixed in food or water, drenched or gavaged, or parenterally. Comparative tests showing the complexing action of urine when 1, 2 and 3 components are administered to both animals and men. 35

CHELATION OR COMPLEXING ACTION OF URINE

Object: To check normal chelation or complexing action of urine and then orally medicate with agents listed below and subsequently check the same animal's new chelation or complexing action of the urine, if any.

A. Chelating Agents (Used)

EDTA (ethylene diamine tetraacetic acid) DTPA (Diethylene triamine pentaacetic acid) HDTA (N-(2-Hydroxyethyl)ethylene diamine triacetic acid) CaEDTA (The Calcium Salt of Ethylenediamine-tetraacetic acid)	non-assimilable
--	-----------------

Complexing Phosphates (Used)

Sodium Tripolyphosphate S.Q. Phosphate Sodium Hexametaphosphate Sodium Acid Pyrophosphate	assimilable
--	-------------

B. Colloidal Gums (Used)

Sodium carboxymethyl cellulose

C. Ion exchange resins (None)

Number of experiments — animals and man: Eighty Three

Sample of Average Results

Complexing Agent or Agents Administered by Mouth	Pre-medication Complexing Value of Urine	2-4 Hrs. Post-Medication Complexing Value of Urine	Evaluation
One Component			
1. 8 gms. EDTA	.32	.15	None
2. 8 gms. Sod. Tripolyphosphate (Form I)	.30	.59	Poor
3. 8 gms. Sod. Carboxymethyl cellulose	.26	.23	None
4. 8 gms. Sod. Hexametaphosphate	.08	.09	None
5. 4 gms. HDTA	.30	.40	None
6. 8 gms. S.Q. Phosphate	.08	.40	Fair
7. 8 gms. Sod. Acid Pyrophosphate	.34	.40	None
8. 4 gms. CaEDTA	.25	.27	None
9. 4 gms. DTPA	.47	.15	None
Three Components			
10. 4 gms. HDTA, 8 gms. Sod. Tripoly (Form I)-8 gms. Sod. Carboxymethyl Cellulose	.24	.50	Fair
Two Components			
11. 4 gms. DTPA, 8 gms. Sod. Tripoly (Form I)	.60	2.20	Very Good
12. 4 gms. EDTA, 8 gms. S.Q. Phosphate	.20	.40	Fair
13. 4 gms. EDTA, 8 gms. Sod. Hexametaphosphate	.16	.20	Poor
14. 4 gms. HDTA, 8 gms. Sod. Hexametaphosphate	.18	1.80	Very Good
15. 4 gms. HDTA, 8 gms. Sod. Acid Pyrophosphate	.25	2.37	Very Good

METHOD OF PROCEDURES:

1. Collect a urine sample from animal and immediately medicate with one of the above agents singly or in combination.

5 2. Assay collected urine specimen immediately for chelation or complexing ability. THIS WAS DONE TO COMPARE ANIMALS NORMAL ABILITY AGAINST INCREASED OR DECREASED VALUE

10 RESULTING FROM MEDICATION.

3. Urine specimens were made alkaline with sodium hydroxide to a pH of 9 and filtered.

4. 1 drop saturated ammonium oxalate solution per cc urine was added.

15 5. Specimen was titrated to first permanent turbidity with a calcium ion-containing solution (1 mg/ml solution).

6. Chelating or complexing ability determined by the amount in ml calcium ion-containing solution required to accomplish permanent turbidity.

20

2 TO 4 HOURS LATER

1. Collected urine specimen from same animal so comparison can be made as to new chelation or complexing ability of urine post-treatment.

25 2. Repeat assay procedure as outlined above for pre-treatment.

Conclusion:

30 1. The urine of many animals has a normal chelation or complexing ability in the urine which probably explains why many animals do not develop renal calculi.

2. Chelating agents administered alone

35 demonstrate some chelating ability in some animals but the chelating agent does not reach a high enough concentration within the body processes to effectively accomplish the dissolution of aberrant cations.

40 3. Sequestering Phosphates administered alone seem to break down into the inactive ortho phosphate form, for the most part.

4. The results of experiments 10-15 demonstrate the synergistic, additive, or protective effect that these complexing agents have with one another when orally administered to animals in combination of two or more complexing agents together.

5. The effects observed were obtained when a naturally assimilable complexing agent was used together with a non-assimilable complexing agent, neither of which was able to produce the effect alone.

6. The oral administration of two assimilable complexing agents of which one may have a greater affinity for cations within the alimentary tract thus forming insoluble intestinal complexes hence allowing the other to be assimilable demonstrated promise in rabbit studies.

45

50

55

60

Effect of Oral Chelating Agents and Inorganic Complexing Phosphates on Complexing Power of Urine

Method:

Base line of normal chelating power of urine at different time intervals established 16 July on four people and one dog.

Three of same people and same dog given various chelating agents by mouth and urine specimen checked at intervals after treatment for chelating power 20 July.

70

Same three people rechecked after taking same chelating agent 23 July.

Chelating powder determined by adjusting pH of urine to about 9, filtering and using 5 cc of filtered urine in following test. 5 drops saturated ammonium oxalate solution added and titrated to 1st permanent turbidity with calcium chloride solution containing 1 mg calcium ion per ml. Results expressed in ml calcium chloride solution required to reach end point.

75

80

16 July, 1961

Name	Medication	Hrs. After Med. Intervals of 2 to 3 Hrs.	Chelating Pr.	Average
Dee (Child)	None	2 to 3 Hrs.	.46 .42 .08 .32	.32
H.A.	None	Same	.08 .28 .32	.23
Dog	None	One Spec. Only	.14	.14
20 July, 1961				
H.A.	3 gm. HDTA 1.2 gm. Sodium hexametaphosphate 1.2 gm Carboxymethyl cellulose .6 gm	2 Hrs. 4 Hrs. 6 Hrs.	.28 .34 .29	.30
Dog	3 gm. HDTA 1.2 gm. Sodium hexametaphosphate 1.2 gm	3 Hrs.	.34	.34
23 July, 1961.				
H.A.	3 gm. HDTA 1.5 gm. Sodium hexametaphosphate 1.5 gm	2 Hrs. 4 Hrs. 6 Hrs.	.60 .54 .18	.44
F.M.	.5 gm. HDTA 2.5 gm. Sodium hexametaphosphate 2.5 gm Divided into two doses at 3 Hr. Intervals	2 Hrs. 3 Hrs. 4 Hrs. 6 Hrs.	.30 .26 .34 .54	.36

Conclusions:

Human urine has normal chelating power.
Young people seem to have more of this ability.

5 The degree of chelating power varies from time to time during the day.

10 Oral administration of various chelating agents and inorganic complexing phosphates enhances the complexing power of both human and canine urine.

*Report on One Case of Human Renal Pelvic Lithiasis (Stag Horn) Treated with RX-1120-C**

15 A 46 year old white female has suffered with chronic pyelonephritis for the past five years. About two and one-half years ago she began developing a right renal pelvic stone

which has gradually grown into a typical stag horn calculus about the size of a lemon. For the past two years she has never been able to go more than ten days without antibiotic and at no time has been really well.

20 About the first of May she was started on 2 capsules (.5gm ea.) of RX-1120-C with each meal. She has experienced no side effects other than mild "heartburn." The really amazing result is that she has required no antibiotic since starting therapy although

25 *FORMULA NO. 1 (RX 1120-C)
HDTA 1 gram
Sodium Tripolyphosphate* 1 gram
Carboxymethylcellulose 1 gram
* or sodium hexametaphosphate

bacilluria and pyuria persist. X-ray shows no change in the size of the stone — but at least it is no larger.

5 *Report on Effect of RX-1120-C on Blood Cholesterol in one Human Subject*

About three years ago a 49 year old white male suffered a coronary thrombosis at which time he was found to have a consistently elevated blood cholesterol of between 400—500 10 mg percent. He was placed on a low cholesterol diet and given various medications with little or no effect on his level.

On July 1, 1961, he was placed on 1 gm 15 RX-1120-C each meal. One week later his blood cholesterol was determined at 242 mg percent, and on July 22, 1961, was found to be 283 mg percent.

20 From this observation on one human subject, it would appear that this preparation has properties capable of lowering blood cholesterol levels superior to the methods now in use. Certainly further evaluation of the material is imperative in view of the gravity of the problem.

25 The results of the following test at the end of a 90 day period demonstrated the lowering of the cholesterol considerably over the controls. Further, the phosphorus level was lowered.

30 *Effect on White Rats of Prolonged Intake of Composition of Invention in Drinking Water*

35 Forty-eight young white rats weighing 340 to 400 grams were placed in wire cages in groups of six per cage. The rats were allowed

two weeks of adjustment and acclimatisation to feeding, watering and environment. The normal intake of water per rat was approximately 50 cubic centimeters per day, taken from a 1 liter flask containing an automatic nipple.

40 Daily dose of a composition of the invention (comprising 85 mg/ml tetrasodium ethylenediamine tetraacetate and 60 mg/ml sodium tripolyphosphate in water) ranging from 4 to 256 minims per day were given by providing corresponding concentrations of the composition (4, 8, 16, 64, 128, 256 minims per 50 ml) in the drinking water.

45 After 90 days, two rats from each group were sacrificed and tissue structures, gonads, skeletal and general anatomy examined for evidence of pathology. None was found. At the end of the 90 day period, the rats receiving 4, 8, 16 and 64 minims per day of the composition were larger and heavier and had more lustrous coats than did the rats receiving 128 and 256 minims per day. The higher concentrations of the composition in the drinking water had made it less palatable and smaller quantities had been consumed causing these rats to show symptoms of dehydration.

50 The remaining rats were continued on the various levels of the composition for a total of 178 days. Then all animals were anesthetized, weighed, bled from the heart ventricle, and euthanized. The blood samples were centrifuged to separate the serum which was submitted to the laboratory for determination of blood levels of calcium, phosphorus, and cholesterol.

40

45

50

55

60

65

70

Group	Composition Dosage Per Day (minims)	Average Weight (Grams)	Blood Calcium (mg %)	Blood Phosphorous (mg %)	Blood Cholesterol (mg %)
1	.4	620	10.8	5.9	57
2	.8	640	10.8	6.3	78
3	16	619	10.8	7.6	90
4	64	579	11.7	7.4	88
5	128	540	10.4	7.8	96
6	.256	505	10.8	7.6	105
7	Control	490	10.8	9.2	112
8	Control	500	10.8	9.3	110

With regard to the treatment of urinary calculi in animals, the following formulae have been found to be very effective:

Formula No. 1 (Rx 1120-C)

HDTA	1 gram
Sodium Tripolyphosphate*	1 gram
Carboxymethylcellulose	1 gram

Formula No. 2

HDTA	1 gram
Sodium Tripolyphosphate*	1 gram
Poly-N-vinyl-5-methyl-2-oxazolidinone	1 gram

Formula No. 3

HDTA	1/2 gram
Sodium Tripolyphosphate*	1 gram
Poly-N-vinyl-5-methyl-2-oxazolidinone	1/2 gram
Carboxymethylcellulose	1 gram

Formula No. 4

HDTA	2 grams
Sodium Tripolyphosphate*	1.5 grams
Carboxymethylcellulose	.5 grams

* or sodium hexametaphosphate

The dosage range of the formulae which is effective yet does not disturb the animal's feed consumption is:

Cattle	3 grams	to	15 grams per day
Sheep	1 gram	to	6 grams per day
Poultry	120 mgs	to	300 mgs per day
Cats	150 mgs	to	300 mgs per day
Dogs	450 mgs	to	4.5 grams per day
Mink	270 mgs	to	300 mgs per day

5. Various weight combinations of assimilable complexing agents and chelating agents and/or ion-exchange materials together with colloidal carriers, may be used, administered in the ranges above according to the particular animal; and whether the use is prophylactic or therapeutic. These materials are blended together. In actual manufacture, one may add two to seven grams inert carrier to each dose of active ingredient. This could cause the finished product to be a bulkier consistency making its administration easier. The finished product is administered to the animal by blending it into the animal's daily ration or by sprinkling it over the animal's food. Dosing in the form of capsules, tablets, or parenteral

10

15

20

administration might be desirable under certain circumstances:

For treatment of active urinary calculi cases, the larger dosage for the species involved would be indicated. For prevention, the smaller dosage for the species involved is indicated. A good ration adequately fortified with vitamins is also indicated.

To illustrate the novel effects of the above compositions, a commercial trial of Formula No. 1 was conducted in a Central California Feed Lot. Five hundred and three head of steers were fed 5 grams of Formula No. 1 per head, per day, for a period of three days. Before the cattle were put on Formula No. 1, one death from urinary calculi had resulted,

25

30

35

16 sixteen cases of urinary calculi had been diagnosed, and two "dribblers" had been marked. At the conclusion of the three day trial, no cattle were showing signs of urinary calculi; the two "dribblers" showed no symptoms of urinary calculi; no new cases had developed. The steers ate the medicated food readily and there were no apparent side effects.

The Formula No. 1 was used as a top dressing to regular feed after being mixed with sun cured alfalfa meal, dehydrated alfalfa meal, stabilized Vitamin A (250,000 units/head/day) plus a feed enhancer.

To further illustrate the effects of the above composition, the following experiments were undertaken:

TEST 1

Date August 11, 1960

Breed Hereford Steers

Weight 1200 lbs.

Age * 18 months — 2 years

Sex Steers

No. of animals 200

History Straining, inappetance, numerous granules on prepuclial hairs. 75 out of 200 demonstrated granules on prepuclial hairs.

Condition Seven animals showing partial urethral obstruction. Two of the seven died.

Symptoms Urine retention — distress

Diagnosis Urinary Calculi

Therapy Antibiotics — depropone (deproteinized pancreatic extract) used from September 16, 1960 to September 21, 1960. One Angus steer showing edema in abdominal wall. Trocar introduced into peritoneal cavity and drained. September 21, 1960 here some improvement but not satisfactory. At this time entire group animals placed on RX 1120—C** in their daily ration.

* Average age of animals if more than one

** RX 1120—C is code for formula No. 1.

Evaluation 4 — 5 days following use of RX 1120—C prepuclial granules were disappearing. And the Angus steer in particular cleared and was on full feed with no apparent symptoms and no further complications. Steer finished out with no more trouble. After discontinuance of RX 1120—C (4 days before marketing) prepuclial granules began to reappear.

TEST II

Breed	Cat
Sex	Male
No. of animals	1
History	Cat entered and condition was diagnosed as urolithiasis. The animal was anaesthetized and catheterized thus allowing free passage of urine from the bladder.
Therapy	The cat was given 10 drops of RX 1120-C Calculi medicine daily. The cat was entered two more times within the next week — each time it was necessary to pass a catheter in order to empty the bladder. Since then the cat has been doing fine and is able to pass his urine freely.
Evaluation	Additional treatment consisted of urisel (a diuretic) administered as 2 pills morning and evening for 10 days.

TEST III

Breed	German Shorthair
Weight	75 lbs.
Sex	Male
No. of Animals	1
History	Was treated for urethral calculi for 4 days. The urethra was flushed and the flow of urine was normal when the case was dismissed. Owner reported two days later that occasionally dog had difficulty urinating and then would pass a small calculus.
Diagnosis	Urethral Calculi
Therapy	20 drops of RX 1120-C Calculi medicine was administered daily. No more difficulty has been reported by the owner. In addition, urisel (a diuretic containing hexamethylene tetramine as active ingredient) was administered as 2 pills morning and evening.
Duration of treatment (total number of days)	20 drops per day until bottle emptied.

TEST IV

Date	October 30, 1960
Breed	Domestic Cat
Weight	9 lbs.
Age	1-1/2 years
Sex	Male
No. of animals	1
History	Frequent urination with blood. Decrease in appetite
Symptoms	Temperature 103.2. Sore abdominal region. Demonstrated pain when bladder was palpated. Small grains of sand at end of penis.
Diagnosis	Urinary Calculi
Therapy	1st day P.M. RX 1120—C — 10 drops 2nd day A.M. 10 drops RX 1120—C 3rd day A.M. 10 drops RX 1120—C 4th day A.M. 10 drops RX 1120—C
Duration of treatment (total number of days)	7
Evaluation	No recurrence of symptoms 28—11—60 still no further complications Cat doing fine.

TEST V

Date	November 26, 1960
Breed	Herefords
Weight	400 lb.
Age*	5 months
Sex	Males
No. of animals	3
History	After weaning, calves were placed on bunker feeding of grains and alfalfa hay with corn silage. Most animals adjusted well, with no apparent indigestion. Three showed signs and developed rumen distention from gas formation. The bloat persisted and became chronic, requiring daily removal of the gas via stomach tube.
Condition	Animals lost weight due to chronic bloating consequently they could not ingest enough nutrients to gain or maintain their weight.
Symptoms	Distended rumen, inappetence, gradual loss of weight
Diagnosis	Chronic Bloat (Tympanitis)
Therapy	Bloat relieved by tube and each animal given RX 1120—C at 5 grams per day for 5 days. 6th day animals were not bloating and appetites were improving. 2 grams RX 1120—C were mixed into each animal's feed per day.
Evaluation	Animals making an uneventful recovery and are still on RX 1120—C.

* average age of animals if more than one

TEST VI

Date	October 14, 1960
Breed	White Faced Sheep
Weight	77 lbs.
Age *	8 months
Sex	Male
No. of animals	12
History	Took two lots of six lambs and placed each lot in separate pens. Made two identical rations but added RX 1120-C to one group's ration which was designated lot No. 1. Group without RX 1120-C was designated lot No. 2. Fed each lot of lambs for 27 days. At time of termination of experiment, for lot one containing RX 1120-C, 207 individual lamb eating days were noted. For lot two without RX 1120-C 199 lamb eating days were noted. Lot one consumed an average of 5.54 lbs. of feed per day. Lot two consumed an average of 3.75 lbs. of feed per day.
Diagnosis	Note: Two lambs were sacrificed from each group on 3/11/60. These were examined for pathogenicity. All were normal. One lamb from lot number 2 was sacrificed on 19/11/60.
Evaluation	RX 1120-C increased feed efficiency by .44 lb. per head per day in careful controlled lamb feeding experiment.

* average age of animals if more than one

TEST VII

Date	October 14, 1960
Breed	Lambs
Weight	77 lbs.
Age	8 months
Sex	Males
No. of animals	12

Experiments commenced in the following two lots of lambs October 14, 1960

History: Lot No. 1

2/11/60 — Lambs seemed contented — no evidence of calciferous material on the hairs of prepuce.
 3/11/60 — Sacrificed two lambs for control study. Bladder of urinary tract were completely normal.
 Grade: 1 — U.S. Choice
 1 — U.S. Good

Lot No. 2

2/11/60 — Noticed accumulation of calciferous material on the prepuce hairs of 4 lambs. Lambs were restless.
 3/11/60 — Sacrificed two lambs for urinary tract examination. Bladder exhibited cysts and was very thin walled. Urine contained 2% small stones.
 Grade: 1 — U.S. Choice
 1 — U.S. Good
 10/11/60 — One Lamb demonstrated dribbling urine excretion. It repeatedly kicked at its stomach. This lamb was sacrificed and the urinary tract inspected. Cysts were evident in the proximal portion of the urethra next to the bladder.
 Grade: U.S. Good

Lot No. 1

18/11/60 — The remaining 4 lambs were sacrificed and the urinary tract examined. In each lamb the urinary tract appeared 100% normal.
 Grade: 3 — lambs U.S. Choice
 1 — Lamb U.S. Prime
 In Lot No. 1, the experiment lasted for 207 individual lamb eating days.

Lot No. 2

18/11/60 — The remaining 3 lambs were sacrificed and urinary tracts inspected. Typical irritation cysts were evident in all three bladders. The upper end of the urethra showed signs of irritation. The urine contained 2% solids in the form of small stones. The Ph was 8.
 Grade: 3 — Lambs U.S. Choice
 In Lot No. 2, the experiment lasted for 199 individual lamb eating days.

Lot No. 1

At time of slaughter, lambs weighed as follows:
 3/11/60 (2 lambs) 164 lbs.
 18/11/60 (4 lambs) 456 lbs.

 620 lbs.

Lot No. 2

At time of slaughter, lambs weighed as follows:
 3/11/60 (2 lambs) 178 lbs.
 10/11/60 (1 lamb) 80 lbs.
 18/11/60 (3 lambs) 330 lbs.

 558 lbs.

Ration

Alfalfa hay	200 lbs.
Beet Pulp, dried	300 lbs.
Linseed Meal	170 lbs.
Oats	150 lbs.
Wheat	150 lbs.
Salt	5 lbs.
K_2HPO_4	25 lbs.
Rx 1120—C	1 lb. <hr/>
(Formula No. 1)	1001 lbs.

Ration

Alfalfa hay	200 lbs.
Beet Pulp, dried	200 lbs.
Linseed Meal	170 lbs.
Oats	150 lbs.
Wheat	150 lbs.
Salt	5 lbs.
K_2HPO_4	25 lbs. <hr/>
	1000 lbs.

Conclusion: Lot No. 1

Bladders, urinary tract and urethra were normal in all lambs upon sacrificing. Rx 1120—C was effective in prevention of urinary calculi.

Conclusion: Lot No. 2

Urinary calculi stones were demonstrated in the bladders of the lambs as they were sacrificed. Many cysts were evident in all bladders. The upper end of the urethra showed signs of irritation. The urine contained 2% solids in the form of stones.

A. Treatment of renal calculi in sheep.

Breed	Lambs
Weight:	77 lbs.
Age:	6 months
Sex	Male
No.	6
History:	Noticed accumulation of calciferous material on the prepuclial hairs on 4 lambs. Lambs were restless and kicked at abdomen.
Condition:	Lambs showed partial urethral obstruction. Bladder extended, with some urine dribbling.
Symptoms:	Urinary retention.
Diagnosis:	Urinary calculi
Therapy:	* 17 1/2 lbs. RX 1120—C mixed in feed plus administering two 1/4 ounce capsules containing Rx 1120—C only once.
Evaluation:	Within 3 days, prepuclial granules had disappeared and animals were urinating normally. There was no further trouble and animals were marketed graded U.S. Choice.

B. Fate of Oral Dosage of Sodium Tripolyphosphate In Human Urine

Samples:

Before Urine 10:20 A.M. color brown 200 ml. vol.

Oral Dosage 20 ml 5% by weight Sodium tripolyphosphate

(1 gram total) 10:30 A.M.

1st After 11:35 A.M. (65 min.) color yellow 100 ml vol

2nd After 12:05 , (95 min.) color straw 50 ml vol

Lunch eaten

3rd After 1:15 P.M. (2 hr. 45 min.) Colorless 200 ml vol

* Composition: RX 1120—C Equal parts Sodium tripolyphosphate and ethylenediaminetetraacetic acid.

Phosphate in urine samples

	Total P	Ortho	Poly
Before Urine	420	480	None
1st After (65 min.)	700	850	None
2nd After (95 min.)	800	800	None
3rd After (2 hr. 45 min.)	530	545	None

Conclusion: Oral dosage of 1 gram of sodium tripolyphosphate resulted in an increase in orthophosphate in the urine with peak at 95 min. sample. There was no detectable polyphosphate in the urine. This suggests conversion of tripolyphosphate to orthophosphate before assimilation. Comparing this result with demonstration of polyphosphate in urine following oral dosage with the formula, we feel this may be evidence for a protective action of

EDTA on tripolyphosphate preventing conversion to orthophosphate by the digestive processes.

5 95 min. sample. There was no detectable polyphosphate in the urine. This suggests conversion of tripolyphosphate to orthophosphate before assimilation. Comparing this result with demonstration of polyphosphate in urine following oral dosage with the formula, we feel this may be evidence for a protective action of

10

Chelating Activity of Urine Samples

Method: 10 ml of sample and 10 ml of 2% by weight sodium carbonate solution is examined for immediate precipitate; if clear, it is titrated with calcium acetate (1 ml = 1 mg Ca)

15

20

Before Urine	ppt forms	none	none
1st After	ppt forms	none	none
2nd After	clear	0.8 ml calcium acetate	5.2 mg/10 ml
3rd After	clear	0.8 ml calcium acetate	5.2 mg/10 ml

Conclusion: In spite of failure of polyphosphate to show in the urine samples, a definite increase in capacity of the urine to hold calcium carbonate in solution is demonstrated in the 2nd and 3rd AFTER samples. The chelating activity is equivalent to 0.5 mg of EDTA per ml which is very low. A test commonly used for demonstrating the chelating activity of EDTA for calcium demonstrates

an increase in chelating activity of urine following oral intake of sodium tripolyphosphate alone. The assimilable complexing agent is present in the urine (as determined by assay) only in the ortho or inactive form. However, only a few parts per million of active polyphosphate are required to exert a sequestering effect.

25

30

35

C. Effect of EDTA on appearance of tripolyphosphate in urine

Schedule: Before Urine 7:45 AM color brown, vol 60 ml

7:45 AM Oral dose: 20 ml 5% by weight EDTA in water and 20 ml 5% by weight sodium tripolyphosphate in water or 1 gram each

1st After: 10:10 AM (2 hr. 25 min.) brown color, 140 ml

2nd After: 11:10 AM (3 hr. 25 min.) yellow color, 60 ml

3rd After: 11:40 AM (3 hr. 55 min.) colorless, 100 ml

Lunch

4th After 1:30 PM (5 hr. 20 min.) yellow color, 140 ml

Fate of Phosphate

	Total ppm	Ortho ppm	Poly. ppm
Before	480	540	None
1st (2 hr. 25 min.)	760	760	None
2nd (3 hr. 25 min.)	840	760	80
3rd (3 hr. 55 min.)	640	560	80
Lunch			
4th (5 hr. 20 min.)	1000	1000	80

5 Conclusions: Appearance of 80 ppm polyphosphate when EDTA and tripolyphosphate are taken together may be compared with previous test where no polyphosphate was found when tripolyphosphate was taken alone.

Chelating Activity
10 ml sample (filtered where necessary to remove natural precipitates; in this case before, 1st and 4th samples were filtered) add 10 ml 2% by weight Na_2CO_3 solution and titrate with Ca acetate 1 ml = 1 mg Ca.

10

Ca mg/10 ml EDTA Equivalent mg.10 ml.

Before	0.3 ml	3.0 mg/10 ml
1st	0.6	6.2
2nd	1.7	11.3 (0.113% EDTA)
3rd	1.3	13.4 (0.134% EDTA)
4th	0.6	6.2

Basis: 1 ml Ca acetate :≡: 1 mg CA :≡: 10 358 mg Na_4EDTA

Conclusion:

A test commonly used for demonstrating the chelating activity of EDTA for calcium demonstrates an increase in chelating activity 5 of urine following oral intake of the formula.

This activity is attributable to the polyphosphate which is assimilable, and not to the EDTA which cannot be assimilated from the gut.

BLADDER STONES IN DOG

History: 3 year old female Pekinese dog was presented demonstrating straining inappetance, and difficulty in voiding urine. Voided urine was bloody in appearance.

Animal had three previous cystotomies for the removal of urinary stones accumulated in the bladder; the last one being 6 months earlier in this clinic. Chemical analysis of these stones revealed a composition of magnesium ammonium phosphate.

Diagnosis: Urinary stones accumulation in the bladder. X-ray of the bladder demonstrated a heavy significant deposit of aberrant cations within the bladder.

Therapy: Animal medicated with 40 drops Rx 1120—C* daily from June 14, 1961 to July 8, 1961. X-ray taken June 26, 1961 revealed some diminution in quantity of stones. On July 8, 1961, therapy was changed to Rx 1120—VH** capsules administering two grams daily. Within two days, urine appeared normal. Two weeks later, July 21, 1961, another X-ray was taken. This plate revealed approximately 2/3 the number of stones visible in earlier X-rays were now dissolved with composition subsequently eliminated.

Evaluation: The Rx 1120—VH capsules appear to have a very significant dissolving action on bladder stones composed of magnesium ammonium phosphate when such capsules are taken by mouth. This material has demonstrated a significant effect on the over-all health of the animal. She has put on weight and visibly has never been in better health.

Conclusion: RX 1120—VH when administered by mouth is effective in dissolving aberrant cation compounds when such compounds are deposited in the bladder of dogs and are composed of magnesium ammonium phosphate.

* Rx 1120—C — Formula No. 1

** Rx 1120—VH — HDTA and Sodium Hexametaphosphate

Evaluation of RX 1120-C as an Additive to Vitamins and Trace
Minerals in Thoroughbred Horses to Potentiate Anti-Anemic Agents

History: Animals had been on a ration highly fortified with vitamins and trace minerals, containing recognized anti-anemic factors such as iron and cobalt, for at least six months prior to testing.

Pre-Treatment: Hemoglobin levels
5 year mare — May 27, 1961 — 15.2 gms/100 cc Blood
June 1, 1961 — 15.2 gms/100 cc Blood
June 9, 1961 — 14.8 gms/100 cc Blood
18 months colt May 27, 1961 — 12.5 gms/100 cc Blood
June 1, 1961 — 12.5 gms/100 cc Blood
June 9, 1961 — 12.1 gms/100 cc Blood

On June 10, 1961 RX 1120-C was added to horses ration with all other factors remaining the same.

Post-Treatment: Hemoglobin levels

5 year mare — July 21, 1961 — 17.7 gms/100 cc Blood
18 months colt July 21, 1961 — 14.5 gms/100 cc Blood

Observations: Both animals have gained considerable weight on the same ration and appear in excellent physical condition. They take the RX-1120 C readily on their grain.

was given intravenously to another dog. Chelating power of pre-treatment urine and post-treatment urines were determined as outlined below.

15

Urine was made alkaline to a pH of about 9, urine was filtered and 5 ml of the filtered urine was used on test material. Five drops saturated ammonium oxalate solution was added to the urine, which was then titrated with calcium chloride solution containing 1 mg calcium ion per ml to first permanent turbidity. Results expressed in ml calcium solution required.

20

25

Effect of Intravenous RX-1120-C and RX-1120-VH on Chelating Power of Dog Urine

Method: A sterile 5% by weight solution of sodium hexametaphosphate with 0.2% by weight HDTA was given intravenously to one dog, and a 5% by weight solution of sodium tripolyphosphate with 0.2% by weight HDTA

Dog No. 1 (wt. 45 lbs.) Medication: 100 cc RX 1120-VH (5 gm sodium hexametaphosphate and 0.2 gm HDTA)

Dog No. 2 (wt. 13 lbs.) Medication: 25 cc RX 1120-C (1.25 gm sodium tripolyphosphate and 0.5 gm HDTA).

	Pre-Treatment	2 hr post Rx	24 hr post Rx	48 hr post Rx
Dog No. 1	.17 ml	2.10 ml	.24 ml	.34 ml
Dog No. 2	.23 ml	1.37 ml	.20 ml	.20 ml

Results: Both dogs exhibited typical hypocalcemia tetany. Dog No. 1 recovered spontaneously on stopping the intravenous preparation, but Dog No. 2 required intravenous

calcium to relieve the condition. Both dogs were apparently completely well and unaffected as soon as the tetany was relieved.

Chelating power of urine was increased 35

1235% in Dog No. 1 and 595% in Dog No. 2 two hours after treatment. Chelating power had dropped back to normal 24 hours later.

Conclusions:

5 Chelating power of dog urine can be greatly enhanced by intravenous administration of chelating agents. To further illustrate the novel effects of this invention, human volunteers suffering from various collagen diseases

10 such as arthritis, osteoporosis and related diseases were administered oral doses of a composition comprising equal amounts of ethylenediamine tetraacetic acid and sodium hexametaphosphate (CURECAL) ranging from

15 625 mgs twice daily to 1875 mgs three times a day. Good results were reported as exhibited by the following cases:

ESTRA + --

W.B.
Age: 53 Sex: M Date: January 10, 1965
20 History: Since released from army service in 1948 has had frequent attack of polyarthritis.
Diagnosis: Polyarthritis.
Previous Treatment: 10 grams of Sodium 25 salicylate was taken every four hours until pain subsided.
Prognosis: Only temporary relief could be expected.
CURECAL medication Began: June 1962
30 Dosage: 2 to 4 grams daily.
Results:
1. Improvement — Polyarthritis has not reoccurred—How Soon — Since CURECAL medication started.
35 2. Other forms of medication — None
3. Pain retarded — None
4. Swelling visibly reduced — No pain or swelling since CURECAL medication started
40 5. Libido — none
6. Nausea — none Vomiting — None — Diarrhea — None
Evaluation: CURECAL has been effective in preventing attacks of polyarthritis

45 *L.S.B.*
Age: 54 Sex: F Date: January 10, 1965
History: Since September 1964 fingers on left hand swollen in joint regions. Had to stop wearing rings.
50 Diagnosis: Rheumatoid arthritis
Previous Treatment: Aspirin, massage and heat all with no lasting effect.
CURECAL medication began: October 3, 1964
55 Dosage: 2 grams morning and night
Results:
1. Improvement — marked How Soon — Second day
2. Other forms of medication — None
60 3. Pain retarded — Pain stopped on second day

4. Swelling visibly reduced
5. Libido — none
6. Nausea — none Vomiting — None
Diarrhea — None

Conclusions: Marked improvement by second day after starting to take CURECAL. Swelling reduced and could get rings on and no pain in fingers.

65

G.S.
Age: 78 Sex: F Date: January 9, 1965
History: Since 1958 have had frequent attacks of arthritis in fingers, back and knee joints. At times pain would be so severe would be confined to bed.
Diagnosis: Rheumatoid arthritis.
Previous Treatment: Aspirin, vitamin B, heat and massage.
Prognosis: Doctor said I just had to learn to live with it.
CURECAL medication Began: October 10, 1964
Dosage: 2 grams twice daily (morning and night)

70

Results:
1. Improvement — Marked How Soon — Second day
2. Other forms of medication — None
3. Pain retarded — only slight pain in back
4. Swelling visibly reduced — Swelling and 90 soreness went away
5. Libido — None
6. Nausea — None Vomiting — None
Diarrhea — None
Conclusions: Can walk with a cane and soreness in all joints subsided, except only very slight pain in back and able to do all own housework.

95

Evaluation: CURECAL has definitely given marked relief from the continuous pain in fingers, knees and back joints.

100

C.A.R.
Age: 58 Sex: M Date January 7, 1965
History: 1945 May — arthritis in arm, hand and shoulder
Diagnosis: Rheumatoid arthritis
Previous Treatment: Gold — cortisone
Prognosis: (Final Projected outcome) — no cure, just adjust to it.
CURECAL medication Began: October 2, 1964
105 Dosage: 3 a day to start, cut to $\frac{1}{2}$
Results:
1. Improvement — Yes How Soon — 60 days
2. Other forms of Medication — aspirin
3. Pain retarded — some
4. Swellings visibly reduced — yes
5. Libido (improved sex relations) — none
6. Side Effects — Nausea — yes Vomiting 120 —no — diarrhea — no

115

120

7.B.C.

Age: 50 Sex: M Date: January 7, 1965
 History: 1947-48, ankle, knees, wrist, elbows
 —days unable to walk — spent 6 months
 5 in bed.

Diagnosis: Rheumatoid Arthritis
 Previous Treatment: Cortisone and therapy
 Prognosis (Final Projected outcome) — no
 cure — just adjust to it

10 CURECAL medication Began: August 13,
 1964
 Dosage: 3 pills per day — cut to one a day
 Results:
 15 1. Improvement — 100% How Soon — 60
 days
 2. Other forms of Medication — none
 3. Pain retarded — yes
 4. Swellings visibly reduced — yes
 5. Libido (improved sex relations) — none
 20 6. Side Effects — diarrhea

It is apparent from the foregoing that there
 is provided a composition and process for pre-
 venting and treating aberrant or undesirable
 25 cation accumulations in the systems of animals
 which cause many well-known ailments such
 as calcific gall stones, renal calculi, calcific
 deposits in bursa, salivary calculi, osteo-
 porosis, collagen diseases, sclerotic or athero-
 30 sclerotic plaques or deposits in blood vessels
 or other organs.

WHAT WE CLAIM IS:—

1. A composition consisting of (a) a non-
 toxic inorganic complexing phosphate selected
 from sodium tripolyphosphate (Form I), sodium
 35 tripolyphosphate (Form II), sodium hexameta-
 pyrophosphate, sodium hexametaphosphate,
 tetrasodium pyrophosphate, tetrapotassium
 pyrophosphate, S.Q. phosphate (as herein
 defined) and sodium acid pyrophosphate
 40 together with (b) a chelating agent selected
 from (I) N,N-di-(2-hydroxyethyl)glycine, the
 sodium salt of N,N-di-(2-hydroxyethyl)glycine,
 N - (2 - hydroxyethyl) ethylene diamine tri-
 acetic acid, trisodium N - (2 - hydroxyethyl)
 45 ethylene diamine triacetate, 1,2-diaminocyclo-
 hexane tetraacetic acid, nitrilotriacetic acid,
 2 - hydroxymethyl - 5 - hydroxy - pyran, and
 N,N,N,N' - tetrakis(2 - hydroxypropyl)
 ethylene diamine or (II) ethylene diamine
 50 tetraacetic acid, the mono-, di-, tri-, and tetra-
 sodium salts of ethylenediamine tetraacetic
 acid, the calcium salt of ethylene diamine
 tetraacetic acid, diethylene triamine penta-
 acetic acid and pentasodium diethylene tri-
 55 amine pentaacetate and/or (c) a non-toxic ion-
 exchange material selected from (III) a resin
 having a carboxylic acid functional group,
 sodium aluminosilicate gel, a polystyrene
 matrix having a nuclear sulphonic acid group
 60 as a functional group, a styrene-divinyl
 benzene copolymer matrix with sulphonic acid
 functional groups, a hydrocarbon matrix

having phosphonic acid groups, a styrene-
 divinyl benzene copolymer matrix with a
 quaternary ammonium functional group and a
 styrene-divinyl benzene copolymer matrix with
 a polyalkylamine functional group or (IV)
 (when the chelating agent, if present, is a
 chelating agent of group (I) poly-N-vinyl-5
 methyl-2-oxazolidinone and copolymers of N-
 vinyl-5-methyl-2-oxazolidinone.

2. A composition according to claim 1
 wherein said chelating agent is a chelating
 agent of group (I) and/or said ion exchange
 material is an ion exchange material of group
 (III) also containing a colloidal carrier.

3. A composition according to claim 2
 wherein said colloidal carrier is sodium car-
 boxymethylcellulose, carboxymethylcellulose or
 other cellulose gum.

4. A composition according to any one of
 the preceding claims also containing water as
 a carrier.

5. A composition according to claim 1 sub-
 stantially as hereinbefore described.

6. A composition comprising (a) a colloidal
 carrier and (b) a non-toxic inorganic complex-
 ing phosphate selected from sodium tripoly-
 phosphate (Form I), sodium tripolyphosphate
 (Form II), sodium hexameta-
 pyrophosphate, sodium hexametaphosphate,
 tetrasodium pyrophosphate, tetrapotassium
 pyrophosphate, S.Q. phosphate (as herein
 defined) and sodium acid pyrophosphate together
 with (c) a chelating agent selected from N,N-di-(2-hydroxyethyl)glycine, the sodium salt of N,N-di-(2-hydroxyethyl)glycine, N - (2 - hydroxyethyl) ethylene diamine triacetic acid, trisodium N - (2 - hydroxyethyl) ethylene diamine triacetate, 1,2 - diaminocyclohexane tetraacetic acid, nitrilotriacetic acid, 2 - hydroxymethyl - 5 - hydroxy - pyran, and N,N,N,N' - tetrakis(2 - hydroxypropyl) ethylene diamine and/or (d)

105 a non-toxic ion-exchange material selected
 from a resin having a carboxylic acid func-
 tional group, sodium aluminosilicate gel, a
 polystyrene matrix having a nuclear sulphonic
 acid group as a functional group, a styrene-
 divinyl benzene copolymer matrix with sul-
 phonic acid functional groups, a hydrocarbon
 matrix having phosphonic acid groups, a
 styrene-divinyl benzene copolymer matrix with
 a quaternary ammonium functional group and a
 styrene-divinyl benzene copolymer matrix
 with a polyalkylamine functional group.

110 7. A composition according to claim 6
 wherein said colloidal carrier is sodium car-
 boxymethylcellulose, carboxymethylcellulose or
 other cellulose gum.

8. A composition according to claim 6 or
 claim 7 also containing water as a carrier.

9. A composition according to claim 6 sub-
 stantially as hereinbefore described.

10. A veterinary method which comprises
 orally administering to animals a composition
 according to any one of the preceding claims.

65

70

75

80

85

90

95

100

105

110

115

120

125

11. A method according to claim 10 substantially as hereinbefore described.

MARKS & CLERK,
Chartered Patent Agents,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which
copies may be obtained.

THIS PAGE BLANK (USPTO)